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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/456,429	12/08/1999	YU-HUA JI	P-015-RP1	6458
27038	7590 10/08/2003		EXAMINER BAKER, MAURIE GARCIA	
THERAVANCE, INC. 901 GATEWAY BOULEVARD SOUTH SAN FRANCISCO, CA 94080			ART UNIT 1639	PAPER NUMBER 24
DATE MAILED: 10/08/2003				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/456,429

Applicant(s)

Ji et al

Examiner

Maurie G. Baker, Ph.D.

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on May 13, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 74-83 is/are pending in the application.
- 4a) Of the above, claim(s) 75-77 and 79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 74, 78, 81, and 83 is/are rejected.
- 7) ☒ Claim(s) 80 and 82 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

DETAILED ACTION

1. The Response filed May 13, 2003 (Paper No. 24) is acknowledged. Claims 74 and 83 were amended and no claims were cancelled or added. Therefore, claims 74-83 are pending.
2. Claims 75-77 and 79 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, there being no allowable generic claim.
3. Thus, claims 74, 78 and 80-83 are currently under examination.

Status of Rejections & Objections

4. The previous objection to claim 83 is withdrawn in view of the amendments thereto. The declaration under 37 CFR 1.132 filed May 13, 2003 is deemed to be sufficient to overcome the rejection of claims 74, 78 and 80-83 under 35 U.S.C. 112, first paragraph. Therefore this rejection is also withdrawn. Also, the previous rejections under 35 U.S.C. 102(b) and under 35 U.S.C. 102/103 are withdrawn in view of applicant's claim amendments.

5. New art rejections based on a non-elected species are set forth in this action.

With respect to the species election and final rejections, see MPEP § 803.02 (emphasis added):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Claim Objections

6. Claims 78 and 80-82 are objected to because of the following informalities: the claims depend from cancelled claim 69. It is believed that this is a typographical error and that the claims should all depend from independent claim 74. Appropriate correction is required.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 74 and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Leung-Toung et al (US 5,723,618).

Leung-Toung et al disclose a compound that reads directly on those of the claims containing two ligands (L) of formula (ii). See columns 1-3; specifically see compound IE at the bottom of columns 5-6, described in Example 3 of the patent. This compound has two ligands reading directly on formula (ii) and the linker in the compound reads on the X of the claims = substituted (-OH) alkylene. The compounds of the reference are based on known calcium channel blockers, (see, e.g., column 1, lines 19-23) and pharmaceutically acceptable salts are made (see, e.g., column 3, lines 16-17), thus a pharmaceutical composition would be anticipated. Alternatively, see paragraph 11 below.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 74 and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Leung-Toung et al (US 5,723,618).

Leung-Toung et al disclose a compound that reads directly on those of the claims containing two ligands (L) of formula (ii). See columns 1-3; specifically see compound IE at the bottom of columns 5-6, described in Example 3 of the patent. This compound has two ligands reading directly on formula (ii) and the linker in the compound reads on the X of the claims = substituted (-OH) alkylene. The compounds of the reference are based on known calcium channel blockers, (see, e.g., column 1, lines 19-23) and pharmaceutically acceptable salts are made (see, e.g., column 3, lines 16-17), thus a pharmaceutical composition would be anticipated.

However, depending on the interpretation of what is part of the L moiety and what constitutes the X group in the instant claims, the compounds of Leung-Toung et al could be interpreted as missing a $-CH_2$ group. If so, the compounds of the reference and the claims would be homologs. Then, the analysis would be that the compounds of the references and of the claims have very close structural similarities and similar utilities (see MPEP § 2144.09 “An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.” *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)).

Moreover, compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Also, alternatively, with respect to the pharmaceutical composition of instant claim 83, since Leung-Toung et al teach that their compounds have biological activity (the compounds of the reference are based on known calcium channel blockers, see, e.g. column 1, lines 19-23), and pharmaceutically

acceptable salts are made (see, e.g., column 3, lines 16-17), the creation of a pharmaceutical composition would be obvious to one of ordinary skill.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention make the instantly claimed homologs (and pharmaceutical compositions thereof) based on the teachings of Leung-Toung et al of compounds having very close structural similarities and similar utilities. One would have been motivated to do so because homologs often have similar properties and therefore one of ordinary skill would ordinarily contemplate making them to obtain compounds with improved properties (i.e. to create more efficacious compounds for treatment).

12. Claims 74, 78, 81 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over either of Yamamori et al (US 5,378,698) or Yamamori et al (US 5,462,936).

Both of the Yamamori et al references disclose dimeric compounds that read directly on the compounds of the instant claims containing one ligand (L) of formula (iv) and one ligand (L) of either of formula (iii) or (v). The moieties in the reference reading on formulas (iv) and either (iii) or (v) are linked by an alkyl linker, reading on the claimed X. Specifically, see compounds in Examples 14 and 24 in each of the patents. See attached printouts from STN included for applicant's convenience. The references also disclose pharmaceutical compositions, see the Abstract of either patent.

It is noted that the compounds specifically exemplified in Examples 14 and 24 of the patents have structural differences from those claimed. Namely, the compounds have a chloro substituent instead of H at the position denoted Y and in Example 24, the compound of the reference also has chloro instead of fluoro on the benzhydryl group. However, it is the examiner's position that the compounds of the claims can be "at once envisaged" from the generic chemical formula disclosed by the Yamamori et al references, see columns 1-2 and especially patented claims of each reference. Note that when the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. See MPEP 2131.02.

In the alternative, if one interprets the compounds of the claims as not being at once envisaged by the above references, the examiner deems that the claimed compounds would be obvious for the following reasons.

The references clearly teach compounds with halogen substitution (i.e. halogen in general and specifically chloro) and the use of any halogen at these positions would be deemed to be *prima facie* obvious due to their art recognized

equivalence. Also, the references clearly teach that hydrogen is a preferred substituent for the Y position as well. See patented claim 1 is the '936 patent. Thus, due to close structural similarities and similar utilities, one would have been motivated to make the claimed compounds based on the teachings of the Yamamori et al references. One of ordinary skill would ordinarily contemplate making such compounds to obtain entities with improved properties (i.e. to create more efficacious compounds for treatment). See MPEP 2144.06 and MPEP 2144.09 with respect to close structural similarity between chemical compounds.

Status of Claims/Conclusion

13. No claims are allowed. However, claims 80 and 82 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner is on an increased flextime schedule but can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

16. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
October 5, 2003



MAURIE GARCIA BAKER PH.D.
PRIMARY EXAMINER